

OFFICE OF THE DIRECTOR OF NATIONAL INTELLIGENCE



The H5N1 Influenza Controversy: Implications for Science Governance

L E A D I N G I N T E L L I G E N C E I N T E G R A T I O N

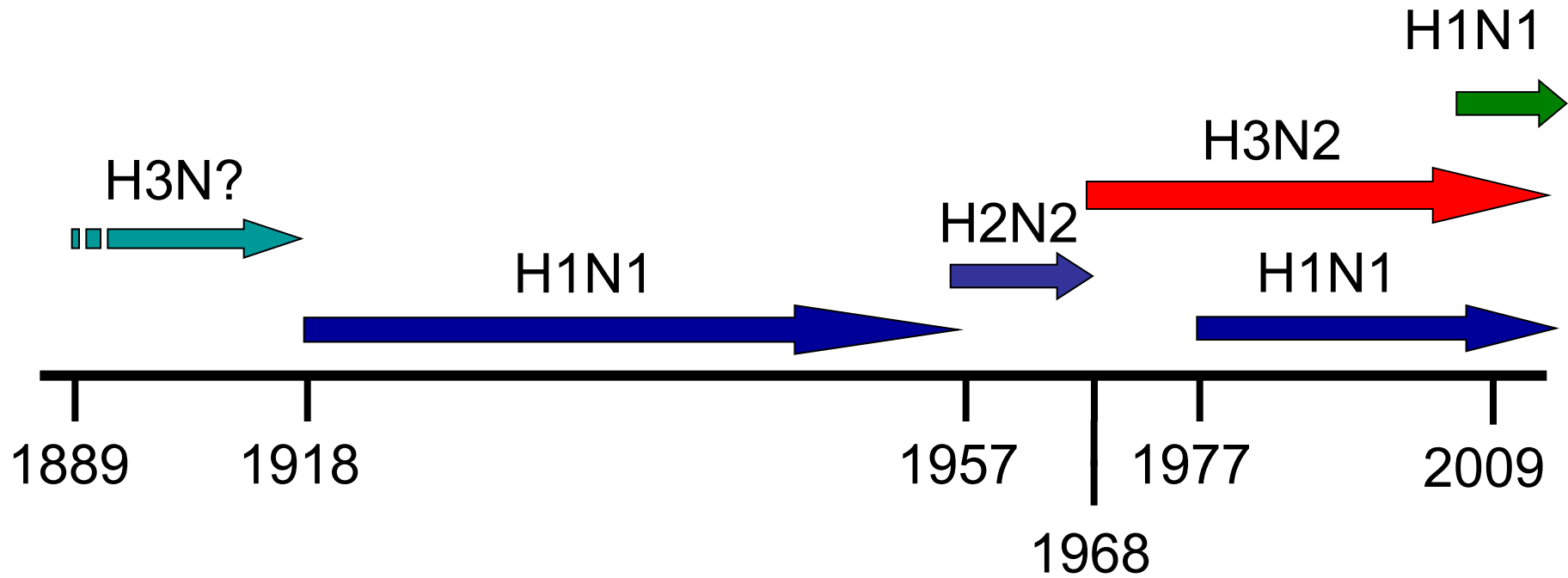
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Agenda:

- 1. H5N1 Influenza**
- 2. Summaries of the aH5N1 Manuscripts**
- 3. US Review of the Manuscripts**
 - **Review processes**
 - **Risk/Benefit Analyses**

Human Influenza A Timeline



Mortality Impacts of Past Influenza Pandemics

1918 “Spanish”
flu (H1N1):

- 50 – 130 M deaths globally

1957 “Asian” flu
(H2N2):

- ~1- 4 M deaths globally

1968 “Hong
Kong” flu (H3N2):

- ~1M deaths globally

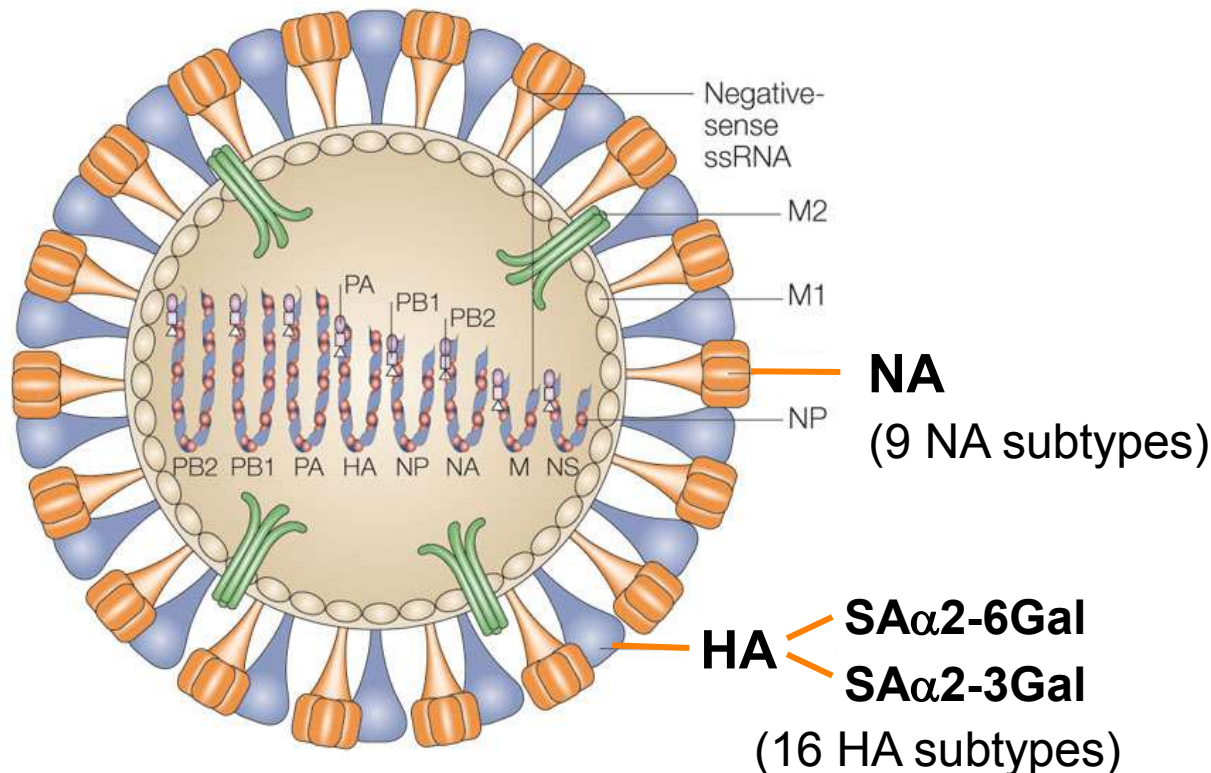
2009 “Swine” flu
(H1N1):

- 300-600 K deaths globally

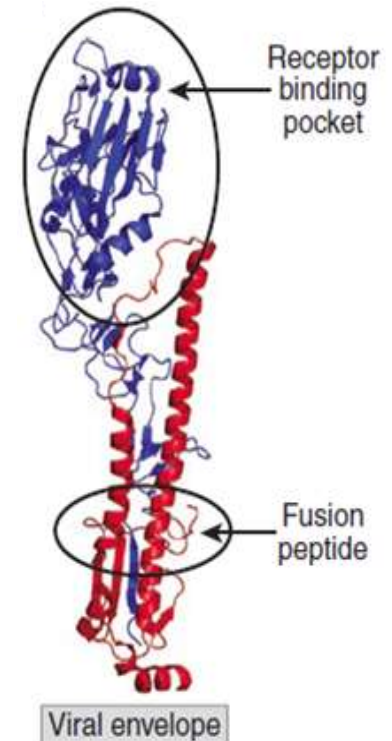
Influenza A virus

✨ Family: lacks proof-reading abilities and is very error-prone; thus “drift” mutants can be selected for:

1. Host switch (jump from birds to pigs to humans)
2. Antiviral drug resistance
3. Antigenic drift (escape from immune detection and elimination)

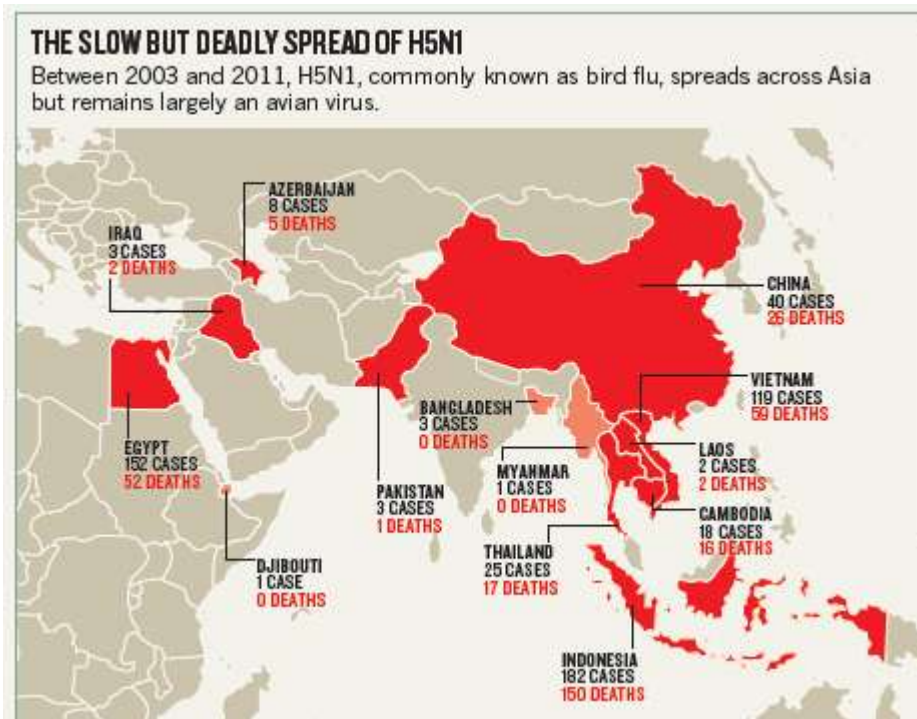


Hemagglutinin (HA)



H5N1 Concerns to Date

- Highly pathogenic avian H5N1 viruses enzootic in poultry in numerous countries; H5N1 found in numerous animal, fowl and wildlife species
- Zoonotic human infections still occurring, with case fatality rate (CFR) ~60% (569 cases with 334 deaths)



- All cases related to direct contact with infected birds
- Occasional, non-sustained human-to-human transmission
- Unclear evidence of evolution towards humans

H5N1 Unknowns

- What mutations allow an avian virus to adapt to humans?
 - Likely independent, polygenic changes with few conserved mutations between independent emergences
 - Could reassortment with other viruses produce a transmissible virus among humans?
- What mutations are related to enhanced pathogenicity?
 - HA cleavage site
 - Polymerase gene complex
 - NS1, PB1-F2 proteins
 - Changes to pathogenicity if virus adapts to humans?

Making Avian H5N1 Transmissible to Mammals: Scientific Manuscripts

Sep 19, 2011 Fouchier presentation at Malta Influenza conference

Sep 26, 2011 New Scientist: Five Easy Mutations to Make Bird Flu a Lethal Pandemic

Oct 4, 2011 US received copy of the Fouchier paper from *Science*

Oct 6, 2011 NIH made aware of Kawaoka paper in preparation for *Nature*

Oct 14, 2011 NSABB H5N1 convened to review papers

Nov 18, 2011 NSABB recommendations delivered to USG

Dec 15, 2011 NSABB Policy Statement sent to Nature and Science

Dec 20, 2011 USG/NIH Press Statement on the NSABB Review of the H5N1 research

Jan 21, 2012 Voluntary Moratorium imposed by the influenza community

Jan 26, 2012 USG releases Dual-Use Research of Concern Policy

Feb 17, 2012 WHO Technical Consultation on H5N1 Research Issues

Apr 2, 2012 Royal Society H5N1 Research: Biosafety, Biosecurity and Bioethics

Apr 20, 2012 Statement from the Sec HHS releasing papers for publication

Apr 23, 2012 International Expert Meeting on H5N1 – the Hague

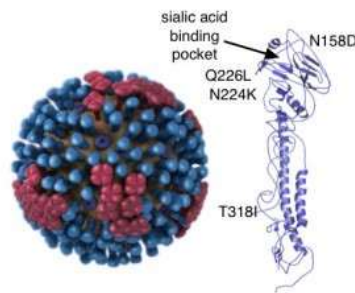
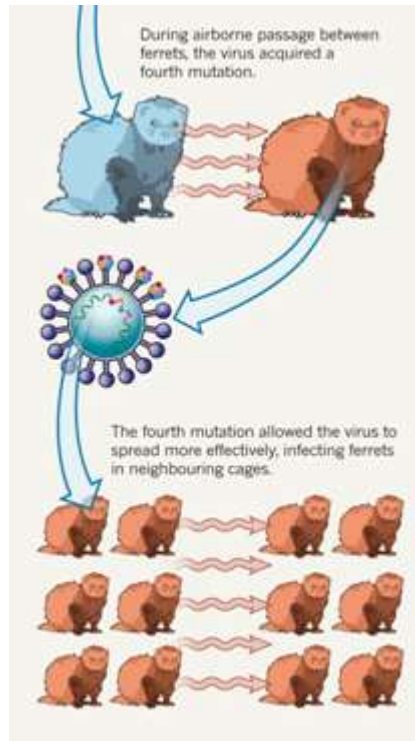
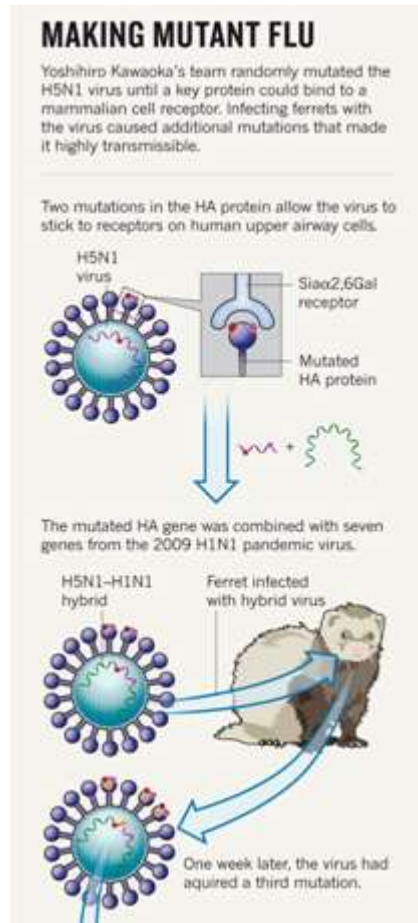
May 1, 2012 US National Academies workshop on H5N1 Research Controversy

May 2, 2012 Kawaoka manuscript published by *Nature* on line

Jun 21, 2012 Fouchier manuscript published in *Science*

Imai, M., et al., Experimental adaptation of an influenza H5 HA confers respiratory droplet transmission to a reassortant H5 HA/H1N1 virus in ferrets

("Kawaoka manuscript," Nature May 2012, 1039 published on line 2 May)



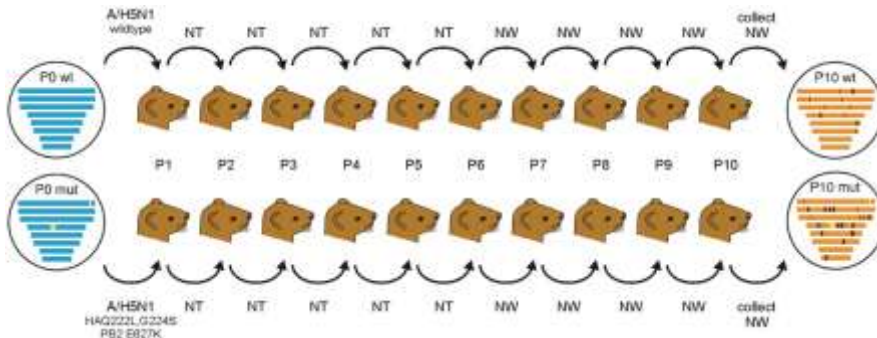
Goal: Test hypothesis that avian H5N1 could be made transmissible to mammals.

Methods: Genetic reassortment of mutant H5N1 HA tested in a 2009 H1N1 human backbone. Mutant viruses subsequently passaged in ferrets.

Results: A reassortant virus with four mutations was identified; the 4 mutants were necessary, but not sufficient for full transmissibility.

Herfst, S., et al., Airborne Transmission of Influenza A/H5N1 Virus Between Ferrets

("Fouchier manuscript," Science 22 June, 2012 Vol. 336 no. 6088 pp. 1534-1541)



Goal: Test hypothesis that avian H5N1 could be made transmissible to ferrets.

Methods: Generated mutant H5N1 HA and PB2 viruses which were subsequently passaged in ferrets. After 10 serial passages, 5 mutations were identified and characterized.

Results: Reassortant viruses with five mutations were identified; the 5 mutants were necessary, but not sufficient for fully sustained transmissibility.

National Science Advisory Board for Biosecurity

- 1. Effective oversight of federally-supported dual-use biological research;**
- 2. The development of a code of conduct for scientists and laboratory workers;**
- 3. Biosecurity training and education for scientists;**
- 4. Publication, public communication and dissemination of dual-use research methodologies and results.**
- 5. Efforts to promote biosecurity principles internationally.**

<http://www.biosecurityboard.gov>

NSABB Expertise

- Molecular/genomics✓
- Microbiology✓
- Clin. ID/diagnostics✓
- Lab biosafety/security✓
- PH/epidemiology✓
- Health physics
- Pharm. production✓
- Veterinary medicine✓
- Plant health✓
- Food production
- Bioethics✓
- National security✓
- Intelligence✓
- Biodefense✓
- IBCs✓
- Export controls
- Law, law enforcement✓
- Scientific publishing✓
- Perspectives from academia, industry, public, RAC ✓

18 NSABB *ex officio*

- Exec. Office of the President
- Department of Health and Human Services (OS, NIH, FDA, CDC)
- Department of Energy
- Department of Homeland Security
- Department of Veteran's Affairs
- U.S. Department of Agriculture
- Department of the Interior
- National Sciences Foundation
- Department of Justice/Federal Bureau of Investigation
- Department of State
- Department of Commerce
- Intelligence Community
- National Aeronautics and Space Administration
- Department of Defense
- Environmental Protection Agency



H5N1 Manuscript(s) Review

Risk Analysis

The findings and/or methods provide sufficient information to pose a threat to public health, agriculture, the economy, or societal well-being. Of particular concern are threats that:

- would cause substantial harm/severe impact
- pose risk to large populations
- require no additional information, or only require information that is already available
- for which there are no countermeasures, or for which existing countermeasures are inadequate in some way (e.g., effectiveness, availability)
- require only readily available materials
- require a low level of expertise to execute
- require low level technology to execute
- can be realized in the immediate or near future

Benefit Analysis

Communication would enable implementation of public health measures, including surveillance and countermeasures

Communication would enable research & development of countermeasures and formulation and implementation of new policies regarding H5N1

Other Considerations

The information is already “out there” and will eventually be disseminated more broadly

In most cases, there are both risks associated with the misuse of information generated from dual use research of concern as well as potential benefits that could be realized from disseminating the information, and decision makers must somehow weigh the potential risks against the anticipated benefits.

In some very rare cases, however, it is conceivable that the risks associated with misuse of information from dual use research of concern are so significant that no amount of potential benefits could possibly outweigh the risks, and consequently *the information should not be communicated*. The conditions under which this could be the case are described under “risk analysis” (above left).

If the above is not the case, then based on a systematic analysis of the risks and benefits and other considerations, there are at least 3 options:

1) COMMUNICATE WITH RESTRICTIONS

2) COMMUNICATE AS IS

3) COMMUNICATE WITH MODIFICATIONS,

- Addition of contextual and clarifying information
- Deletion of methods & materials
- With or without mutation sites

H5N1 MANUSCRIPTS RISK/BENEFIT ANALYSES

Risk Analysis

The manuscripts provide novel scientific information, frameworks for approaches (but not blueprints) for producing pool of recombinant H5N1 viruses with high pathogenicity & sustained, respiratory transmissibility in mammals.

Information in the manuscripts could be used to infer vulnerabilities in public health/safety preparedness (i.e., need for surveillance & improved antivirals and vaccines) that could be exploited for nefarious purposes.

Information from the manuscripts could be directly misused to pose a threat to public health, agriculture, plants, animals, the environment, or materiel—in the near term with respect to replicating the experiments and in the longer term with respect to creating a specific H5N1 virus that is both transmissible and pathogenic among humans.

There is substantial potential for public concern and misunderstanding and great potential for sensationalism if the information in the manuscripts is broadly communicated “as is.”

Benefit Analysis

The manuscripts provide information important to pandemic preparedness efforts, i.e., underscores need for improved surveillance, to maintain vaccine/antiviral stockpiles, & to develop improved countermeasures.

Information in the manuscripts could possibly apply to other animals (influence agricultural practices & responsible use of vaccination for H5N1 susceptible animals), & motivate veterinary, agriculture, & wildlife officials & scientists to prioritize H5N1 epizootics preparedness.

Information in the manuscripts could enhance scientific understanding of respiratory transmissibility & advance public health through development of new antiviral approaches.

Information in the manuscripts could have an immediate, beneficial impact by catalyzing improved public health infrastructure, countermeasure development, surveillance; other potential benefits—new antiviral agents—would be realized years from now.

Statement by NIH Director Francis Collins, MD, PhD on the NSABB Review of Revised H5N1 Manuscripts

April 20, 2012

“On March 29 and 30, the National Science Advisory Board for Biosecurity (NSABB), an independent expert committee that advises the National Institutes of Health (NIH), the Department of Health and Human Services (HHS) and other Federal departments and agencies on matters of biosecurity, convened to review unpublished revised manuscripts describing NIH-funded research on the transmissibility of H5N1 influenza virus—the strain commonly referred to as “bird flu.”

After careful deliberation, the NSABB unanimously recommended the revised manuscript by Dr. Yoshihiro Kawaoka be communicated in full. The NSABB also recommended, in a 12-to-6 decision, that the data, methods, and conclusions presented in the revised manuscript by Dr. Ron Fouchier be communicated fully after a number of further scientific clarifications are made in the manuscript. The HHS Secretary and I concur with the NSABB’s recommendation that the information in the two manuscripts should be communicated fully and we have conveyed our concurrence to the journals considering publication of the manuscripts.

The Secretary’s decision takes account of relevant U.S. law, international obligations, and a rigorous analysis of the benefits and risks of publication.”



Science Safety Security

Finding the Balance Together

